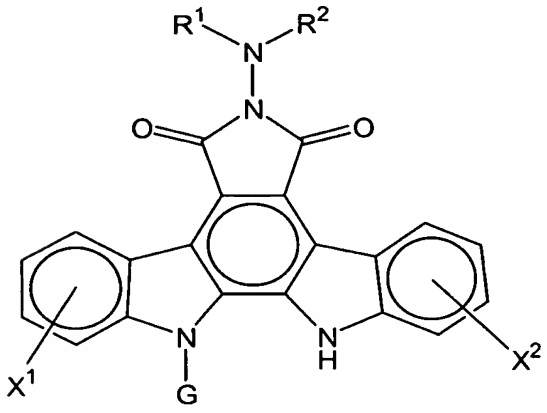
Copy of IB 308, Substitute pages 35 - 53.

Claim 1. A combined preparation for simultaneous, separate, or sequential administration in the treatment of cancer, comprising two separate preparations:

(a) a first preparation comprising, in combination with a pharmaceutically acceptable carrier or diluent, at least one compound of general formula I:



[I]

wherein R^1 and R^2 each independently represent:

a hydrogen atom, lower alkyl, lower alkenyl, lower alkynyl, aryl, aralkyl, or heterocyclic group(wherein the lower alkyl, the lower alkenyl, the lower alkynyl, the aryl, the aralkyl, and the heterocyclic group may each have one to five of the same or different substituents selected from the group consisting of carboxyl, carbamoyl, sulfo, amino, cyano, mono-lower alkylamino, di-lower alkylamino, hydroxyl, and a halogen atom);

or a group of formula -Y-R^3 wherein Y represents carbonyl, thiocarbonyl, or sulfonyl, and R^3 represents a hydrogen atom, lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, aryl, aralkyl, lower alkoxy, hydrazino, amino, arylamino, carbamoyl, or heterocyclic group (wherein the lower alkyl, the cycloalkyl, the cycloalkyl-lower alkyl, the aryl, the aralkyl, and the heterocyclic group may each have one to four of the same or different substituents selected from the group consisting of a halogen

atom, optionally protected hydroxyl, amino, carboxyl, carbamoyl, cyano, and lower alkoxycarbonyl in which the amino and the carbamoyl may each be further mono- or di-substituted by lower alkyl optionally substituted by a substituent or substituents selected from the group consisting of a halogen atom, hydroxyl, amino, carboxyl, carbamoyl, and lower alkoxycarbonyl); or

a group of formula $-(CH_2)_m-R^4$ {wherein R^4 is pyridyl, furyl, or thienyl (wherein the pyridyl, the furyl, and the thienyl may each have one or two substituents selected from the group consisting of hydroxyl, lower alkoxy, hydroxy-lower alkyl, and hydroxy-lower alkenyl), and m is an integer of 1 to 3,

R^1 and R^2 are combined together to represent lower alkylidene (wherein the lower alkylidene may have one to four of the same or different substituents selected from the group consisting of amino, mono-lower alkylamino, di-lower alkylamino, hydroxyl, carboxyl, and sulfo), or

R^1 and R^2, together with the nitrogen atom to which they bind, form heterocyclic group (wherein the heterocyclic group may have, on said ring, lower alkyl optionally substituted by a group or groups selected from the group consisting of amino, hydroxyl, carboxyl, and sulfo),

G represents a pentosyl or hexosyl; and

X^1 and X^2 each independently represent a hydrogen atom, a halogen atom, amino, mono-lower alkylamino, di-lower alkylamino, hydroxyl, lower alkoxy, aralkoxy, carboxyl, lower alkoxycarbonyl, or lower alkyl

or a pharmaceutically acceptable salt thereof; and

(b) a second preparation comprising, in combination with a pharmaceutically acceptable carrier or diluent, at least one antitumor agent selected from the group consisting of antitumor alkylating agents, antitumor antimetabolites, antitumor

antibiotics, plant-derived antitumor agents, antitumor platinum-complex compounds, antitumor campthotecin derivatives, antitumor tyrosine kinase inhibitors, monoclonal antibodies, interferons, biological response modifiers, and other antitumor agents or a pharmaceutically acceptable salt thereof

(wherein the antitumor alkylating agents are nitrogen mustard N-oxide, cyclophosphamide, ifosfamide, melphalan, busulfan, mitobronitol, carboquone, thiotepa, ranimustine, nimustine, or temozolomide,

the antitumor antimetabolites are methotrexate, 6-mercaptopurine riboside, mercaptopurine, 5-fluorouracil, tegafur, doxifluridine, carmofur, cytarabine, cytarabine ocfosfate, enocitabine, S-1, gemcitabine, or fludarabine,

the antitumor antibiotics are actinomycin D, doxorubicin, daunorubicin, neocarzinostatin, bleomycin, peplomycin, mitomycin C, aclarubicin, pirarubicin, epirubicin, zinostatin stimalamer, or idarubicin,

the plant-derived antitumor agents are vincristine, vinblastine, vindeshine, etoposide, sobuzoxane, docetaxel, paclitaxel, or vinorelbine,

the antitumor platinum-complex compounds are cisplatin, carboplatin, nedaplatin, or oxaliplatin,

the antitumor campthotecin derivatives are irinotecan, topotecan, or campthotecin,

the antitumor tyrosine kinase inhibitors are Iressa or SU5416,

the monoclonal antibodies are IMC-C225, RhuMabVEGF, or Rituximab,

the interferons are interferon α, interferon α-2a, interferon α-2b, interferon β, interferon γ-1a, or interferon γ-n1,

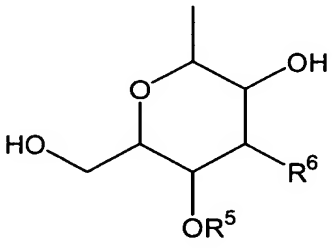
the biological response modifiers are krestin, lentinan, sizofiran, picibanil, or ubenimex, and

the other antitumor agents are mitoxantrone, L-asparaginase, procarbazine, dacarbazine, hydroxycarbamide, pentostatin, or tretinoin).

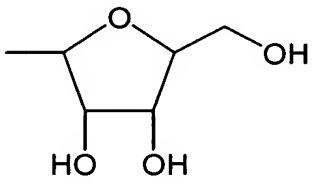
Claim 2. The combined preparation for simultaneous, separate, or sequential administration in the treatment of cancer of claim 1, comprising the first preparation and the second preparation,

wherein the antitumor agent described in the paragraph (b) is selected from the group consisting of: 5-fluorouracil; S-1; gemcitabine; doxorubicin and etoposide; docetaxel and paclitaxel; cisplatin, carboplatin, and oxaliplatin; irinotecan, topotecan, and campthotecin; Iressa and SU5416; and IMC-C225 and RhuMabVEGF or a pharmaceutically acceptable salt thereof (wherein, if said preparation contains 5-fluorouracil, it may further contain leucovorin or may be combined with a separate leucovorin preparation).

Claim 3. The combined preparation as defined in Claim 2, wherein G is a group of formula:



or



wherein R^5 represents a hydrogen atom or lower alkyl, and R^6 represents hydroxyl or amino.

Claim 4. The combined preparation as claimed in Claim 3, wherein X^1 and X^2 bind to the indolopyrrolocarbazole ring at the 1- or 2-position and at the 10- or 11-position, respectively, and each independently represent a halogen atom, hydroxyl, lower alkoxy, or aralkoxy.

Claim 5. The combined preparation as claimed in Claim 4, wherein G is β-D-glucopyranosyl, and X^1 and X^2 represent hydroxyl bonded to the indolopyrrolocarbazole ring at the 2-position and at the 10-position, respectively.

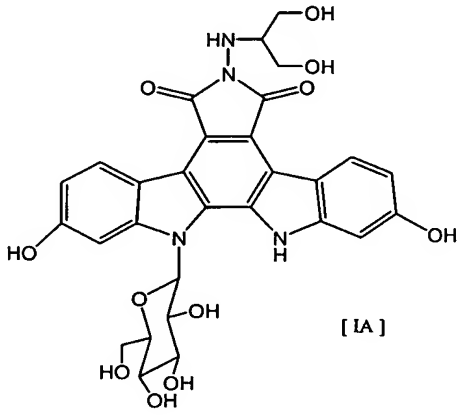
Claim 6. The combined preparation as claimed in Claim 5, wherein R^1 represents a hydrogen atom, and R^2 represents a group of formula:

Claim 7. The combined preparation as claimed in Claim 5, wherein R^1 represents a hydrogen atom, and R^2 represents $-CH_2-R^4$ in which R^4 represents 6-hydroxymethylpyridin-2-yl.

Claim 8. The combined preparation as claimed in Claim 5, wherein R^1 represents a hydrogen atom, and R^2 represents $-CH_2-R^4$ in which R^4 represents pyridin-4-yl.

Claim 9. The combined preparation as claimed in Claim 5, wherein R^1 represents a hydrogen atom, and R^2 represents $-CH_2-R^4$ in which R^4 represents 5-hydroxymethylpyridin-4-yl.

Claim 10. The combined preparation as claimed in Claim 1 or 2, wherein the compound of general formula I described in the paragraph (a) is the compound of formula IA:



[IA]

Claim 11. The combined preparation as claimed in Claim 10, wherein one of or both of the two separate preparations is/are parenteral preparation(s).

Claim 12. The combined preparation as claimed in Claim 11, wherein one of or both of the two separate preparations is/are an injection or an infusion.

Claim 13. The combined preparation as claimed in Claim 12, which is further combined with at least one preparation comprising, in combination with a pharmaceutically acceptable carrier or diluent, at least one antitumor agent selected from the group consisting of antitumor alkylating agents, antitumor antimetabolites,

antitumor antibiotics, plant-derived antitumor agents, antitumor platinum-complex compounds, antitumor campthotecin derivatives, antitumor tyrosine kinase inhibitors, monoclonal antibodies, interferons, biological response modifiers, and other antitumor agents wherein the antitumor alkylating agents are nitrogen mustard N-oxide, cyclophosphamide, ifosfamide, melphalan, busulfan, mitobronitol, carboquone, thiotepa, ranimustine, nimustine, or temozolomide,

the antitumor antimetabolites are methotrexate, 6-mercaptopurine riboside, mercaptopurine, 5-fluorouracil, tegafur, doxifluridine, carmofur, cytarabine, cytarabine ocfosfate, enocitabine, S-1, gemcitabine, or fludarabine,

the antitumor antibiotics are actinomycin D, doxorubicin, daunorubicin, neocarzinostatin, bleomycin, peplomycin, mitomycin C, aclarubicin, pirarubicin, epirubicin, zinostatin stimalamer, or idarubicin,

the plant-derived antitumor agents are vincristine, vinblastine, vindeshine, etoposide, sobuzoxane, docetaxel, paclitaxel, or vinorelbine,

the antitumor platinum-complex compounds are cisplatin, carboplatin, nedaplatin, or oxaliplatin,

the antitumor campthotecin derivatives are irinotecan, topotecan, or campthotecin,

the antitumor tyrosine kinase inhibitors are Iressa or SU5416,

the monoclonal antibodies are IMC-C225, RhuMabVEGF, or Rituximab,

the interferons are interferon α, interferon α-2a, interferon α-2b, interferon β, interferon γ-1a, or interferon γ-n1,

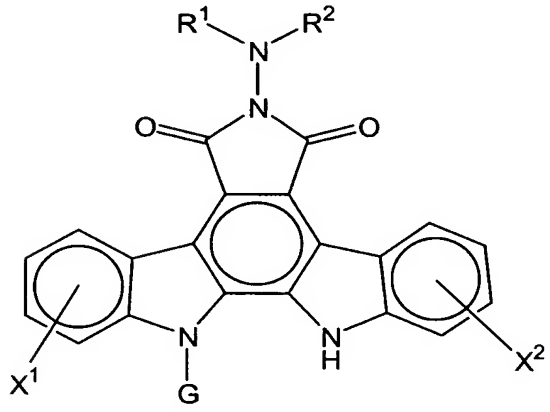
the biological response modifiers are krestin, lentinan, sizofiran, picibanil, or ubenimex, and

the other antitumor agents are mitoxantrone, L-asparaginase, procarbazine, dacarbazine, hydroxycarbamide, pentostatin, or tretinoin,

or a pharmaceutically acceptable salt thereof.

Claim 14. A method for cancer treatment, comprising simultaneously, separately or sequentially administering to a cancer patient:

(a) a therapeutically effective amount of at least one compound of general formula I:



[I]

wherein R^1 and R^2 each independently represent:

a hydrogen atom, lower alkyl, lower alkenyl, lower alkynyl, aryl, aralkyl, or heterocyclic group(wherein the lower alkyl, the lower alkenyl, the lower alkynyl, the aryl, the aralkyl, and the heterocyclic group may each have one to five of the same or different substituents selected from the group consisting of carboxyl, carbamoyl, sulfo, amino, cyano, mono-lower alkylamino, di-lower alkylamino, hydroxyl, and a halogen atom);

or a group of formula -Y-R^3 wherein Y represents carbonyl, thiocarbonyl, or sulfonyl, and R^3 represents a hydrogen atom, lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, aryl, aralkyl, lower alkoxy, hydrazino, amino, arylamino, carbamoyl, or heterocyclic group (wherein the lower alkyl, the cycloalkyl, the cycloalkyl-lower alkyl, the aryl, the aralkyl, and the heterocyclic group may each have one to four of

the same or different substituents selected from the group consisting of a halogen atom, optionally protected hydroxyl, amino, carboxyl, carbamoyl, cyano, and lower alkoxycarbonyl in which the amino and the carbamoyl may each be further mono- or di-substituted by lower alkyl optionally substituted by a substituent or substituents selected from the group consisting of a halogen atom, hydroxyl, amino, carboxyl, carbamoyl, and lower alkoxycarbonyl); or

a group of formula $-(CH_2)_m-R^4$ wherein R^4 is pyridyl, furyl, or thienyl (wherein the pyridyl, the furyl, and the thienyl may each have one or two substituents selected from the group consisting of hydroxyl, lower alkoxy, hydroxy-lower alkyl, and hydroxy-lower alkenyl), and m is an integer of 1 to 3,

R^1 and R^2 are combined together to represent lower alkylidene (wherein the lower alkylidene may have one to four of the same or different substituents selected from the group consisting of amino, mono-lower alkylamino, di-lower alkylamino, hydroxyl, carboxyl, and sulfo), or

R^1 and R^2, together with the nitrogen atom to which they bind, form heterocyclic group (wherein the heterocyclic group may have, on said ring, lower alkyl optionally substituted by a group or groups selected from the group consisting of amino, hydroxyl, carboxyl, and sulfo),

G represents a pentosyl or hexosyl; and

X^1 and X^2 each independently represent a hydrogen atom, a halogen atom, amino, mono-lower alkylamino, di-lower alkylamino, hydroxyl, lower alkoxy, aralkoxy, carboxyl, lower alkoxycarbonyl

or a pharmaceutically acceptable salt thereof;

and

(b) a therapeutically effective amount of at least one antitumor agent selected from the group consisting of antitumor alkylating agents, antitumor antimetabolites, antitumor antibiotics, plant-derived antitumor agents, antitumor platinum-complex compounds, antitumor campthotecin derivatives, antitumor tyrosine kinase inhibitors, monoclonal antibodies, interferons, biological response modifiers, and other antitumor agents

(wherein the antitumor alkylating agents are nitrogen mustard N-oxide, cyclophosphamide, ifosfamide, melphalan, busulfan, mitobronitol, carboquone, thiotepa, ranimustine, nimustine, or temozolomide,

the antitumor antimetabolites are methotrexate, 6-mercaptopurine riboside, mercaptopurine, 5-fluorouracil, tegafur, doxifluridine, carmofur, cytarabine, cytarabine ocfosfate, enocitabine, S-1, gemcitabine, or fludarabine,

the antitumor antibiotics are actinomycin D, doxorubicin, daunorubicin, neocarzinostatin, bleomycin, peplomycin, mitomycin C, aclarubicin, pirarubicin, epirubicin, zinostatin stimalamer, or idarubicin,

the plant-derived antitumor agents are vincristine, vinblastine, vindeshine, etoposide, sobuzoxane, docetaxel, paclitaxel, or vinorelbine,

the antitumor platinum-complex compounds are cisplatin, carboplatin, nedaplatin, or oxaliplatin,

the antitumor campthotecin derivatives are irinotecan, topotecan, or campthotecin,

the antitumor tyrosine kinase inhibitors are Iressa or SU5416,

the monoclonal antibodies are IMC-C225, RhuMabVEGF, or Rituximab,

the interferons are interferon α, interferon α-2a, interferon α-2b, interferon β, interferon γ-1a, or interferon γ-n1,

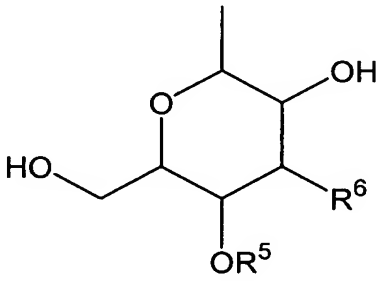
the biological response modifiers are krestin, lentinan, sizofiran, picibanil, or ubenimex, and

the other antitumor agents are mitoxantrone, L-asparaginase, procarbazine, dacarbazine, hydroxycarbamide, pentostatin, or tretinoin)

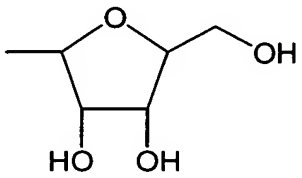
or a pharmaceutically acceptable salt thereof.

Claim 15. The method of claim 14, wherein the antitumor agent described in the paragraph (b) is selected from the group consisting of: 5-fluorouracil; S-1; gemcitabine; doxorubicin and etoposide; docetaxel and paclitaxel; cisplatin, carboplatin, and oxaliplatin; irinotecan, topotecan, and campthotecin; Iressa and SU5416; and IMC-C225 and RhuMabVEGF or a pharmaceutically acceptable salt thereof (wherein, if the compound of general formula I as defined herein is combined with 5-fluorouracil, leucovorin may be further combined).

Claim 16. The method as claimed in Claim 15, wherein G is a group of formula:



or

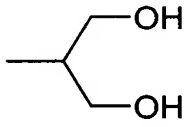


wherein R^5 represents a hydrogen atom or lower alkyl, and R^6 represents hydroxyl or amino.

Claim 17. The method as claimed in Claim 16, wherein X^1 and X^2 bind to the indolopyrrolocarbazole ring at the 1- or 2-position and at the 10- or 11-position, respectively, and each independently represent a halogen atom, hydroxyl, lower alkoxy, or aralkoxy.

Claim 18. The method as claimed in Claim 17, wherein G is β-D-glucopyranosyl, and X^1 and X^2 represent hydroxyl bonded to the indolopyrrolocarbazole ring at the 2-position and at the 10-position, respectively.

Claim 19. The method as claimed in Claim 18, wherein R^1 represents a hydrogen atom, and R^2 represents a group of formula:

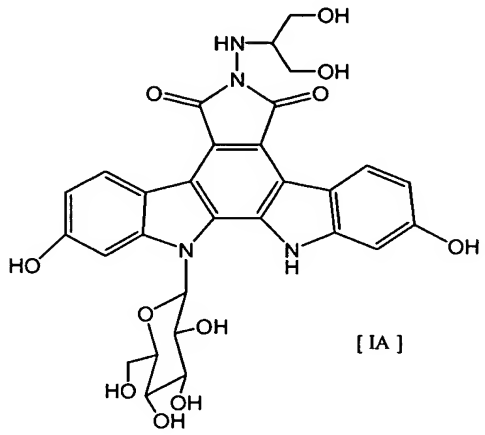


Claim 20. The method as claimed in Claim 18, wherein R^1 represents a hydrogen atom, and R^2 represents $-CH_2-R^4$ in which R^4 represents 6-hydroxymethylpyridin-2-yl.

Claim 21. The method as claimed in Claim 18, wherein R^1 represents a hydrogen atom, and R^2 represents $-CH_2-R^4$ in which R^4 represents pyridin-4-yl.

Claim 22. The method as claimed in Claim 18, wherein R^1 represents a hydrogen atom, and R^2 represents $-CH_2-R^4$ in which R^4 represents 5-hydroxymethylpyridin-4-yl.

Claim 23. The method as claimed in Claim 14 or 15, wherein the compound of general formula I described in the paragraph (a) is the compound of formula IA:



[IA]

Claim 24. (Cancelled).

Claim 25. (Cancelled).

Claim 26. (Cancelled).

Claim 27. (Cancelled).

Claim 28. (Cancelled).

Claim 29. (Cancelled).

Claim 30. (Cancelled).

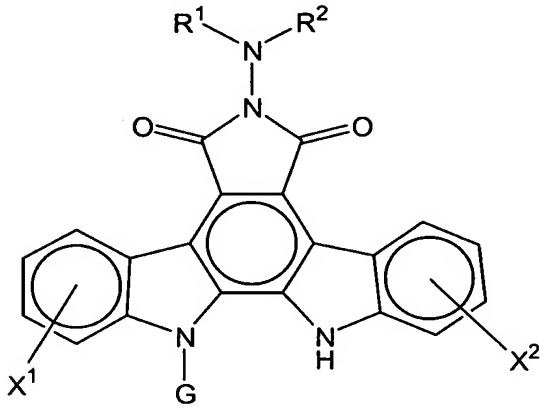
Claim 31. (Cancelled).

Claim 32. (Cancelled).

Claim 33. (Cancelled).

Claim 34. A pharmaceutical composition comprising, in combination with a pharmaceutically acceptable carrier or diluent,

(a) a therapeutically effective amount of at least one compound of general formula I:



[I]

wherein R^1 and R^2 each independently represent:

a hydrogen atom, lower alkyl, lower alkenyl, lower alkynyl, aryl, aralkyl, or heterocyclic group(wherein the lower alkyl, the lower alkenyl, the lower alkynyl, the aryl, the aralkyl, and the heterocyclic group may each have one to five of the same or different substituents selected from the group consisting of carboxyl, carbamoyl, sulfo, amino, cyano, mono-lower alkylamino, di-lower alkylamino, hydroxyl, and a halogen atom);

or a group of formula -Y-R^3 wherein Y represents carbonyl, thiocarbonyl, or sulfonyl, and R^3 represents a hydrogen atom, lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, aryl, aralkyl, lower alkoxy, hydrazino, amino, arylamino, carbamoyl, or heterocyclic group (wherein the lower alkyl, the cycloalkyl, the cycloalkyl-lower alkyl, the aryl, the aralkyl, and the heterocyclic group may each have one to four of the same or different substituents selected from the group consisting of a halogen atom, optionally protected hydroxyl, amino, carboxyl, carbamoyl, cyano, and lower

alkoxycarbonyl in which the amino and the carbamoyl may each be further mono- or di-substituted by lower alkyl optionally substituted by a substituent or substituents selected from the group consisting of a halogen atom, hydroxyl, amino, carboxyl, carbamoyl, and lower alkoxycarbonyl); or

a group of formula $-(CH_2)_m-R^4$ wherein R^4 is pyridyl, furyl, or thienyl (wherein the pyridyl, the furyl, and the thienyl may each have one or two substituents selected from the group consisting of hydroxyl, lower alkoxy, hydroxy-lower alkyl, and hydroxy-lower alkenyl), and m is an integer of 1 to 3,

R^1 and R^2 are combined together to represent lower alkylidene (wherein the lower alkylidene may have one to four of the same or different substituents selected from the group consisting of amino, mono-lower alkylamino, di-lower alkylamino, hydroxyl, carboxyl, and sulfo), or

R^1 and R^2, together with the nitrogen atom to which they bind, form heterocyclic group (wherein the heterocyclic group may have, on said ring, lower alkyl optionally substituted by a group or groups selected from the group consisting of amino, hydroxyl, carboxyl, and sulfo),

G represents a pentosyl or hexosyl; and

X^1 and X^2 each independently represent a hydrogen atom, a halogen atom, amino, mono-lower alkylamino, di-lower alkylamino, hydroxyl, lower alkoxy, aralkoxy, carboxyl, lower alkoxycarbonyl

or a pharmaceutically acceptable salt thereof; and

(b) a therapeutically effective amount of at least one antitumor agent selected from the group consisting of antitumor alkylating agents, antitumor antimetabolites, antitumor antibiotics, plant-derived antitumor agents, antitumor platinum-complex compounds, antitumor campthotecin derivatives, antitumor tyrosine kinase inhibitors,

monoclonal antibodies, interferons, biological response modifiers, and other antitumor agents or a pharmaceutically acceptable salt thereof

(wherein the antitumor alkylating agents are nitrogen mustard N-oxide, cyclophosphamide, ifosfamide, melphalan, busulfan, mitobronitol, carboquone, thiotepa, ranimustine, nimustine, or temozolomide,

the antitumor antimetabolites are methotrexate, 6-mercaptopurine riboside, mercaptopurine, 5-fluorouracil, tegafur, doxifluridine, carmofur, cytarabine, cytarabine ocfosfate, enocitabine, S-1, gemcitabine, or fludarabine,

the antitumor antibiotics are actinomycin D, doxorubicin, daunorubicin, neocarzinostatin, bleomycin, peplomycin, mitomycin C, aclarubicin, pirarubicin, epirubicin, zinostatin stimalamer, or idarubicin,

the plant-derived antitumor agents are vincristine, vinblastine, vindeshine, etoposide, sobuzoxane, docetaxel, paclitaxel, or vinorelbine,

the antitumor platinum-complex compounds are cisplatin, carboplatin, nedaplatin, or oxaliplatin,

the antitumor campthotecin derivatives are irinotecan, topotecan, or campthotecin,

the antitumor tyrosine kinase inhibitors are Iressa or SU5416,

the monoclonal antibodies are IMC-C225, RhuMabVEGF, or Rituximab,

the interferons are interferon α, interferon α-2a, interferon α-2b, interferon β, interferon γ-1a, or interferon γ-n1,

the biological response modifiers are krestin, lentinan, sizofiran, picibanil, or ubenimex, and the other antitumor agents are mitoxantrone, L-asparaginase, procarbazine, dacarbazine, hydroxycarbamide, pentostatin, or tretinoin).

Claim 35. The pharmaceutical composition of claim 34 wherein the at least one antitumor agent described in the paragraph (b) is selected from the group consisting of 5-fluorouracil; S-1; gemcitabine hydrochloride; doxorubicin hydrochloride and etoposide; docetaxel hydrate and paclitaxel; cisplatin, carboplatin, and oxaloplatin; irinotecan, topotecan, and campthotecin; Iressa and SU5416; IMC-C225 and RhuMabVEGF or a pharmaceutically acceptable salt thereof (wherein, if said composition contains the compound of general formula I and 5-fluorouracil, it may further contain leucovorin).